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(54) **Aryloxphenylpropylamines and their preparation and use.**

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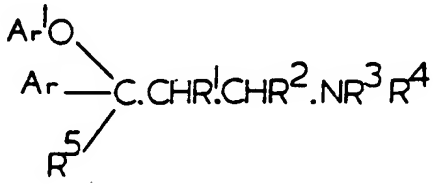
EP 0 318 727 B1

Description

The present invention relates to therapeutically active aryloxyphenylpropylamines, a method of preparing the same and to pharmaceutical compositions comprising the compounds. The novel compounds are useful in the treatment of anoxia, ischemia, migraine and epilepsy.

It is known in the prior art that various aryloxyarylpropylamines have pharmaceutical properties:

GB-A-2 060 622 discloses 3-aryl-3-aryloxy-propylamines of the general formula



wherein R^1, R^2, R^4 and R^5 are hydrogen or lower alkyl, R^3 is hydrogen, lower alkyl or benzyl, Ar is phenyl optionally substituted by one or more halogen, trifluoromethyl, lower alkyl, lower alkoxy, nitro or amino groups and Ar^1 is methylsulphilyl, methylsulphonyl- or cyano-substituted phenyl,2- or 4-pyridyl,2-pyrazinly,2-quinolinyl, 2-thienyl or 2-thiazolyl

which exhibit activity on the central nervous system, e.g. as anti-depressants.

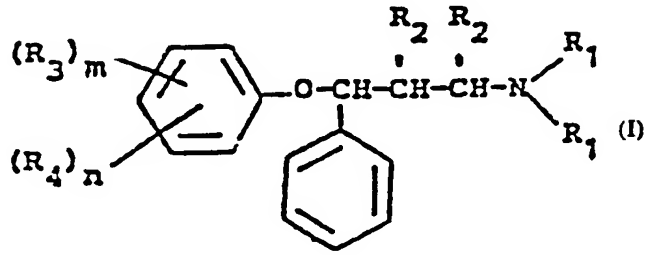
EP-A-0 031 885 discloses "basic ethers" of the general formula (I)

I

wherein Z can inter alia be CH_3-NR^2-CH_2CH_2-CHR^1-.

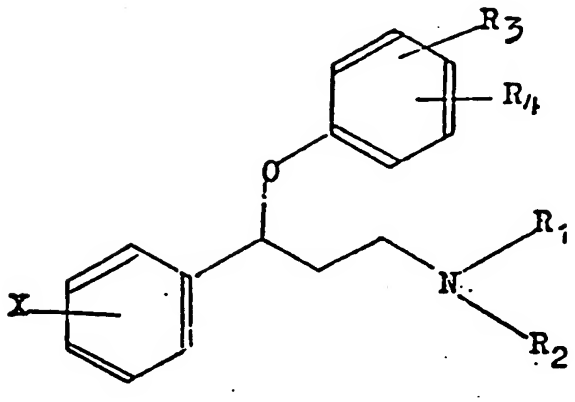
R^1 is defined as cyclopropyl or aryl and R^2 as H, C_{1-4}-alkyl, C_{2-4}-alkenyl, C_{4-8}-cycloalkylalkyl or benzyl. It is stated that the compounds of formula (I) have effects on the central nervous system.

CH-A-609 331 discloses a process for preparing 3-aryloxy-3-phenyl- alkylamines of the general formula (I)



wherein R_1 and R_2 are H or methyl, R_3 and R_4 are halogen, trifluoromethyl, C_{2-4}-alkyl, C_{1-3}-alkoxy or C_{3-4}-alkenyl and n and m can be 0, 1 or 2, provided that the sum of n and m is not 0 if both substituents R_1 are methyl and both substituents R_2 are H. The compounds are described as having effects on the central nervous system and with an analeptic effect.

DE-A-2 907 217 discloses compounds of the general formula (I')



(I')

wherein X is H, F, Cl or Br, R_1 is H or C_{1-5}-alkyl, R_2 is C_{1-5}-alkyl and R_3 is H, Cl or Br, trifluoromethyl, methyl or methoxy and R_4 is nitro, or R_3 is amino or acetamido and R_4 is H. It is mentioned that some of the compounds are used for the treatment of e.g. depression, melanchelia and manic-depression psychoses.

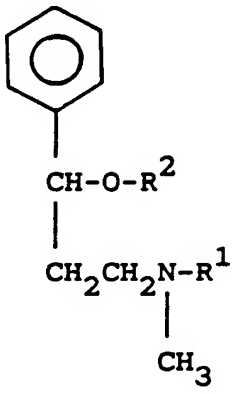
It is well known that accumulation of calcium in the brain cells (calcium overload) is seen after periods of uncontrolled hyperactivity in the brain, such as after convulsions, migraine, anoxia and ischemia. As the concentration of calcium in the cells is of vital importance for the regulation of cell function, an uncontrolled high concentration of the cell calcium will lead to, or indirectly cause the symptoms and possibly also the degenerative changes combined with the above diseases.

Therefore calcium overload blockers selective for brain cells will be useful in the treatment of anoxia, ischemia, migraine and epilepsy.

Well known calcium antagonists such as nifedipine, verapamil and diltiazem have activity against pheripheral calcium uptake, e.g. in blood vessels and the heart, however have shown only very low activity against calcium overload in brain cells.

Accordingly it is an object of the invention to provide novel compounds having activity against calcium overload in brain cells.

The compounds of the invention are aryloxyphenylpropylamines having the general formula I



(I)

wherein

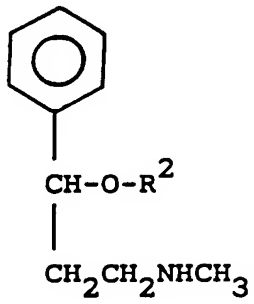
R^1 is C_{3-7}-cycloalkyl, C_{3-10}-alkyl, or alkenyl which may be straight, branched or cyclic, unsubstituted or substituted with C_{1-4}-alkoxy, aryloxy or cycloalkyl or cycloalkylalkyl; and

R^2 is 3,4-methylenedioxyphenyl, aryl or heteroaryl, which are optionally substituted with one or more cyano, halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkenyl, trifluoromethyl, C_{3-5}-alkylene, aryloxy or aralkoxy and salts thereof with a pharmaceutically acceptable acid.

Examples of such salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate, or similar pharmaceutically-acceptable inorganic or organic acid addition salts.

The invention also relates to a method of preparing the above mentioned compounds.This methods comprises

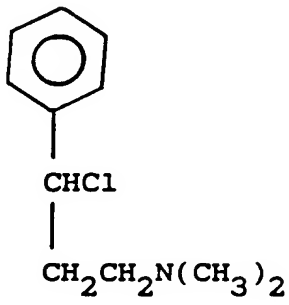
a) reacting a compound having the general formula II



(II)

wherein R^2 has the meaning defined above, with a compound having the the general formula R^1-X, wherein X is a leaving group such as halogen and R^1 has the meaning defined above, and optionally reacting the resulting product with a pharmaceutically acceptable acid.

b) reacting a compound having the formula III

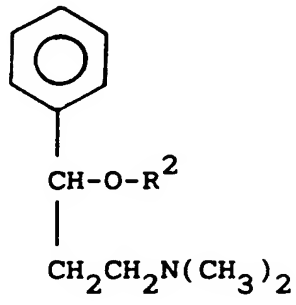


(III)

with a compound having the formula IV

R^2OH (IV)

wherein R^2 has the meaning defined above, giving compounds of the general formula V



(V)

and

c) preparing compounds having the formula III from the corresponding hydroxy compound by means of $SOCl_2$. The hydroxy compounds being prepared by a $NaBH_4$ reduction of the corresponding oxo-compound, which is prepared by a Mannich reaction

d) preparing compounds of the general formuia II by demethylating compounds of the general formuia V by means of $ClCOOCHClCH_3$.

The pharmacological properties of the compounds of the invention can be illustrated by determining their capability to inhibit calcium uptake into brain synaptosomes.

PRINCIPLE

Depolarization of neuronal membranes leads to an opening of socalled 'voltage operated calcium channels' (VOC) in the membranes which allows a massive influx of calcium from the extracellular space. A crude synaptosomal preparation (socalled P_2 fraction) contains small vesicles surrounded by neuronal membrane and it is possible in such a preparation to study a depolarization-induced opening of VOC. In the present model ^{45}Ca influx is induced in the synaptosomes by depolarization with elevated potassium concentrations, and the effect of test substances on this stimulated uptake is studied (Nachshen, D.A. and Blaustein, M.P., Mol. Pharmcol., 16, 579 (1979)).

ASSAY

A male Wistar rat is decapitated and the cerebral cortex removed and homogenized in 20 ml. of ice-cold 0.32 M sucrose using a glass homogenizer with a teflon pestle. All subsequent steps for isolation of synaptosomes are done at 0-4 °C. The homogenate is centrifuged at 1000 x g for 10 min and the resulting supernatant is re-centrifuged at 18000 x g for 20 min. This pellet (P_2) is resuspended in 0.32 M sucrose (10 ml per g of original tissue) with a teflon pestle.

Aliquots (0.050 ml) of this crude synaptosomal suspension are added to glass tubes containing 0.625 ml of NaCl buffer (136 mM NaCl, 4 mM KCl, 0.35 mM $CaCl_2$, 1.2 mM $MgCl_2$, 20 mM Tris HCl, 12 mM glucose, pH 7.4) and 0.025 ml of various drug solutions in 48% Ethanol. The tubes are pre-incubated for 30 min on ice and then for 6 min at 37 °C in a water bath.

The uptake is immediately initiated by adding 0.4 ml of $^{45}CaCl_2$ (specific activity = 29-39 Ci/g; 0.5 Ci/assay), in 145 mM NaCl for non-depolarized samples and in 145 mM KCl for depolarized samples. The incubation is continued for 15 s.

The uptake is terminated by rapid filtration through GF-C glass fiber filters which are washed three times with 5 ml of a cold solution containing 145 mM KCl, 7 mM EGTA and 20 mM Tris HCl, pH 7.4. The amount of radioactivity on the filter disc is determined by liquid scintillation spectrometry.

TEST PROCEDURE

Test substances are dissolved in 10 ml of 48% ethanol at a concentration of 0.44 mg/ml. Dilution are made in 48% ethanol to give final concentrations of 0.1, 0.3, 1, 3 and 10 µg/ml. Experiments are performed in duplicate. Controls for depolarized and nondepolarized samples are included in the assay and test substances are only tested in depolarized samples.

RESULTS

The test value will be given as MEC (the minimum concentration (µg/ml) of test substance which inhibit stimulated uptake of ^{45}Ca significantly different from control ($P < 0.05$, Student's t-test).

Test results obtained by testing some compounds of the present invention will appear from the following table 1.

TABLE 1

Compound	MEC (μg/ml)
1	3.0
2	1.0
3	0.3
4	0.3
16	0.3
17	0.3
22	>1.0
Verapamil*	10
Nifedipin*	>10
Diltiazem*	>10

*well known calcium antagonist

The compound of the invention, together with a conventional adjuvant, carrier, or diluent, and if desired in the form of a pharmaceutically-acceptable acid addition salt thereof, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids, such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective calcium overload blocking amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing ten (10) milligrams of active ingredient or, more broadly, ten (10) to hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of this invention can thus be used for the formulation of pharmaceutical preparations, e.g. for oral and parenteral administration to mammals including humans, in accordance with conventional methods of galenic pharmacy.

Conventional excipients are such pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral or enteral application which do not deleteriously react with the active compounds.

Examples of such carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Ampoules are convenient unit dosage forms.

Tablets,dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch, are particularly suitable for oral application. A syrup, elixir of the like can be used in cases where a sweetened vehicle can be employed.

Generally, the compounds of this invention are dispensed in unit form comprising 0.05-100 mg in a pharmaceutically acceptable carrier per unit dosage.

The dosage of the compounds according to this invention is 0.1-300 mg/day, preferably 10-100 mg/day, when administered to patients, e.g. humans, as a drug.

A typical tablet which may be prepared by conventional tabletting techniques contains:

Active compound	5.0 mg
Lactosum	67.8 mg Ph.Eur.
Avicel®	31.4 mg
Amberlite® IRP 88	1.0 mg
Magnesii stearas	0.25 mg Ph.Eur.

Due to the high calcium overload blocking activity , the compounds of the invention are extremely useful in the treatment of symptoms related to an accumulation of calcium in brain cells of mammals , when administered in an amount effective for blocking calcium overload in brain cells . The important calcium overload blocking activity of compounds of the invention includes both activity against anoxia, ischemia, migraine and epilepsy . The compounds of the invention may accordingly be administered to a subject, e.g., a living animal body, including a human, in need of a calcium overload blocker , and if desired in the form of a pharmaceuticallyacceptable acid addition salt thereof (such as the hydrobromide, hydrochloride, or sulfate, in any event prepared in the usual or conventional manner, e.g., evaporation to dryness of the free base in solution together with the acid), ordinarily concurrently, simultaneously, or together with a pharmaceutically-acceptable carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parenteral (including subcutaneous) route, in an effective calcium overload blocking amount, and in any event an amount which is effective for the treatment of anoxia, ischemia, migraine or epilepsy due to their calcium overload blocking activity. Suitable dosage ranges are 0.1-300 milligrams daily, preferably 10-100 milligrams daily, and especially 30-70 milligrams daily, depending as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and the preference and experience of the physician or veterinarian in charge.

The invention will now be described in further detail with reference to the following examples:

EXAMPLE 1

(+-)N-methyl-N-pentyl-3-phenyl-3-(4-trifluoromethylphenoxy)propylamine, maleinate (Compound 1)

The title compound was prepared from (+-)-N-Methyl-N-(3-phenyl-3-(4-trifluoromethylphenoxy)propyl)-amine, hydrochloride (1 g), potassium carbonate (2 g) and bromopentane (1 ml) by reflux in abs. ethanol (50 ml) for 40 h. The mixture was cooled, acetone/ether (1/1) (50 ml) was added and the mixture was filtered. The filtrate was evaporated to dryness and subsequently suspended in dilute NaOH-solution and extracted with ether. The ether layer was dried ($MgSO_4$) and evaporated to dryness. The title compound was precipitated as the maleinate in acetone solution. M.p. 99 °C.

The following compounds were obtained in exactly the same way as above by reaction with the appropriate bromo compound instead of bromopentane.

(+-)N-methyl-3-phenyl-N-propyl-3-(4-trifluoromethylphenoxy)-propyl, oxalate (Compound 2)

Reflux time 9 h. Precipitated as the oxalate in acetone solution. M.p. 167-9 °C.

(+-)N-butyl-N-methyl-3-phenyl-3-(4-trifluoromethylphenoxy)propylamine, oxalate (Compound 3)

Reflux time 22 h. Purification of the free amine on a silicagel column using CH_2Cl_2 as eluent. Crystallized as the oxalate from acetone/ether. M.p. 160-2 °C.

(+-)N-cyclopropylmethyl-N-methyl-3-phenyl-3-(4-trifluoromethylphenoxypropylamine, oxalate (Compound 4)

Reflux time 4 h. The oxalate crystallized from acetone/ether. M.p. 148,4 °C.

(+-)N-allyl-N-methyl-3-phenyl-3-(4-trifluoromethylphenoxy)propylamine, oxalate (Compound 5)

Equimolar amounts of amine and alkylbromide was used. Reflux time 1 h, RT 16 h. M.p. 104.5 °C.

(+-)N-5-hexenyl-N-methyl-N-(3-phenyl-3-(4-trifluoromethylphenoxy)propylamine, oxalate (Compound 6)

Reflux time 19 h. The oxalate crystallized from acetone/ether. M.p. 126.1 °C.

(+-)N-2-ethoxyethyl-N-methyl-3-phenyl-3-(4-trifluoromethylphenoxy)propylamine, oxalate (Compound 7)

Reflux time 120 h. M.p. 127.5 °C.

(+-)N-methyl-N-(4-phenoxybutyl)-3-phenyl-3-(4-trifluoromethylphenoxy)propylamine, oxalate (Compound 8)

Reflux time 140 h. Purification of the free amine on a silicagel column using CH_2Cl_2/CH_3OH (9:1) as eluent. M.p. 95.7 °C.

(+-)N-methyl-N-(2-methylpropyl)-3-phenyl-3-(4-trifluoromethylphenoxy)propylamine, oxalate (Compound 9)

Reflux time 48 h. Purification of the crude product on silicagel column using CH_2Cl_2/CH_3OH (9:1) as eluent. M.p. 169.5 °C.

EXAMPLE 2

(+-)3-dimethylamino-1-phenyl-1-propanol (Compound 10)

β-dimethylaminopropiophenone (20.3 g) was dissolved in abs. ethanol, sodium borohydride (1.09 g) was added and the mixture was stirred at RT for 19 h. Subsequently the reaction mixture was evaporated to dryness; the residue was extracted with H_2O/diethylether. The combined etheral layers were dried ($MgSO_4$), filtration and evaporation gave (10) as a yellow oil identified by its ^1H NMR spectrum.

(+-)3-chloro-N,N-dimethyl-3-phenylpropylamine, hydrochloride (Compound 11)

(+-)3-dimethylamino-1-phenyl-1-propanol (10) (19 g) was dissolved in CH_2Cl_2 (200 ml). The solution was saturated with HCl (g). Thionyl chloride (17 ml) was added dropwise over 20 min. resulting in slight reflux. Subsequental reflux for 5 h resulted in the formation of a precipitate. Cooling and evaporation of the reaction mixture resulted in a yellowish crystalline mass, which was rinsed by several washings with acetone, resulting in colourless crystals of the title compound identified by ^1H NMR.

(+-)N,N-dimethyl-3-phenyl-3-(5,6,7,8-tetrahydro-2-naphthoxy)propylamine, oxalate (Compound 12)

5,6,7,8-tetrahydro-2-naphthol (7.4 g) and NaOH (2 g) was dissolved in abs. ethanol (100 ml) by stirring at RT. When all was dissolved compound (11) (6 g) was added and the mixture refluxed for 120 h. The mixture was evaporated to dryness, the residue extracted from 4 M NaOH/diethylether. The combined ether layers were dried ($MgSO_4$), filtered and the filtrate evaporated to dryness yielding an oil. The oil was precipitated as the oxalate by mixing equimolar amounts of anhydrous oxalic acid and free amine. M.p. 164.4 °C.

(+-)N-methyl-3-phenyl-3-(5,6,7,8-tetrahydro-2-naphthoxy)propylamine, oxalate (Compound 13)

Compound (12) as the free base (2 g) was dissolved in dry 1,2-dichloroethane (30 ml). 1-chloroethyl chloroformate (0.76 ml) was added dropwise under cooling. The solution was refluxed for 1 h, evaporated to dryness. Methanol (50 ml) was added, and the solution refluxed for 3 h. Subsequent evaporation, extraction from 4M NaOH/ether gave a yellow oil after evaporation of the ether layer. Precipitation in acetone solution by mixing equimolar amounts of amine and anhydrous oxalic acid. M.p. 190.2 °C.

The following compounds were prepared from compound (13) as described in example 1, compound 1.

(+-)N-methyl-N-pentyl-3-phenyl-3-(5,6,7,8-tetrahydro-2-naphthoxy)propylamine, oxalate (Compound 14)

Reflux time 7 h. M.p. 168.4 °C.

(+-)N-cyclopropylmethyl-N-methyl-3-phenyl-3-(5,6,7,8-tetrahydro-2-naphthoxy)propylamine, oxalate (Compound 15)

Reflux time 4.5 h. M.p. 134.8 °C.

(+-)N-butyl-N-methyl-3-phenyl-3-(5,6,7,8-tetrahydro-2-naphthoxy)propylamine, oxalate (Compound 16)

Reflux time 18 h. M.p. 160.8 °C.

(+-)N-methyl-N-(2-methylpropyl)-3-phenyl-3-(5,6,7,8-tetrahydro-2-naphthoxy)propylamine, oxalate (Compound 17)

Reflux time 48 h. M.p. 153.2 °C.

(+-)N-methyl-3-phenyl-N-propyl-3-(5,6,7,8-tetrahydro-2-naphthoxy)propylamine, oxalate (Compound 34)

Reflux time 6 h. Purification on silica gel column with CH_2Cl_2/CH_3OH (9:1) as eluent. M.p. 169.1-169.7 °C.

EXAMPLE 3

(+-)N,N-dimethyl-3-(3,4-methylenedioxyphenoxy)-3-phenylpropylamine, oxalate (Compound 18)

Preparation from compound (11) and 3,4-methylenedioxyphenol as described for compound (12). M.p. 96.9 °C.

(+-)N-methyl-3-(3,4-methylenedioxyphenoxy)-3-phenylpropylamine, oxalate (Compound 19)

Preparation from (18) and $ClCOOCHClCH_3$ as described for compound (13) with the exception that sodium dried toluene was used as solvent instead of 1,2-dichloroethane. Heating in toluene at 80 °C for 2 h. M.p. 148.7 °C.

(+-)N-cyclopropylmethyl-N-methyl-3-(3,4-methylenedioxyphenoxy)-3-phenylpropylamine, oxalate (Compound 20)

Prepared from compound (19) and bromomethylcyclopropane using the method described for compound (1). Reflux time 4.5 h. M.p., 150.0 °C.

(+-)N-butyl-N-methyl-3-(3,4-methylenedioxyphenoxy)-3-phenylpropylamine, oxalate (Compound 21)

Preparation from compound (19) and 1-bromobutane as described for compound (1). Reflux time 19 h. M.p. 127.0 °C.

EXAMPLE 4

(+-)3-(5-indanyloxy)-N,N-dimethyl-3-phenylpropylamine, oxalate (Compound 22)

Prepared from compound (11) and 5-indanol by reflux for 75 h as described for compound (12). M.p. 153.2 °C.

(+-)3-(5-indanyloxy)-N-methyl-3-phenylpropylamine, oxalate (Compound 23)

Preparation from compound (22) and $ClCOOCHClCH_3$ as described for compound (19). M.p. 161.4 °C.

(+-)N-butyl-3-(5-indanyloxy)-N-methyl-3-phenylpropylamine, oxalate (Compound 24)

Prepared from compound (23) and 1-bromobutane as described for compound (1). M.p. 172.5 °C.

(+-)N-cyclopropylmethyl-3-(5-indanyloxy)-N-methyl-3-phenylpropylamine, oxalate (Compound 25)

Prepared from compound (23) and bromomethylcyclopropane as described for compound (1). M.p. 175.8 °C.

EXAMPLE 5

(+-)N,N-dimethyl-3-phenyl-3-(3-trifluoromethylphenoxy)propylamine, oxalate (Compound 26)

Prepared from compound (11) and 3-trifluoromethylphenol by reflux for 75 h, as described for compound (12). M.p. 167.7 °C.

(+-)N-methyl-3-phenyl-3-(3-trifluoromethylphenoxy)propylamine, oxalate (Compound 27)

Prepared from compound (26) by means of $ClCOOCHClCH_3$ as desribed for compound (19). M.p. 157.7 °C.

(+-)N-butyl-N-methyl-3-phenyl-3-(3-trifluoromethylphenoxy)propylamine, oxalate (Compound 28)

Preparation as described for compound (1) from 1-bromobutane and (27). M.p. 153.2 °C.

(+-)N-cyclopropylmethyl-N-methyl-3-phenyl-3-(3-trifluoromethylphenoxy)propylamine, oxalate (Compound 29)

Prepared from compound (27) and bromomethylcyclopropane as described under (1). M.p. 150.6 °C.

EXAMPLE 6

(+-)3-(2-cyanophenoxy)-N,N-dimethyl-3-phenylpropylamine, oxalate (Compound 30)

The compound was prepared from (11) and 2-cyanophenol as described for (12) by reflux for 10 h. M.p. 138-43 °C.

EXAMPLE 7

(+-)N,N-dimethyl-3-(2-methylphenoxy)-3-phenylpropylamine, oxalate (Compound 31)

Preparation from (11) and 2-methylphenol by reflux for 27 h as described for compound (12). M.p. 169-171 °C.

EXAMPLE 8

(+-)3-(2-methoxyphenoxy)-N,N-dimethyl-3-phenylpropylamine, oxalate (Compound 32)

Preparation from (11) and 2-methoxyphenol by reflux for 1 h as described for compound (12). M.p. 127-130 °C.

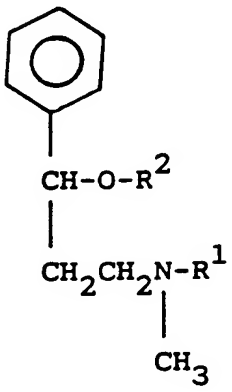
(+-)N-butyl-N-methyl-3-(2-methoxyphenoxy)-3-phenylpropylamine, oxalate (Compound 33)

Prepared from N-methyl-3-(2-methoxyphenoxy)-3-phenylpropylamine and 1-bromobutane by reflux in ethanol solution for 10 h as described for compound (1). M.p. 102-6 °C.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Aryloxyphenylpropylamines having the general formula I



(I)

wherein
R^1 is C_{3-7}-cycloalkyl, C_{3-10}-alkyl or alkenyl which may be straight, branched or cyclic, unsubstituted or substituted with C_{1-4}-alkoxy, aryloxy or cycloalkyl or cycloalkylalkyl; and
R^2 is 3,4-methylenedioxyphenyl, aryl or heteroaryl, which are optionally substituted with one or more cyano, halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkenyl, trifluoromethyl, C_{3-5}-alkylene, aryloxy or aralkoxy;
and salts thereof with a pharmaceutically acceptable acid.

2. A compound of claim 1 which is N-butyl-N-methyl-3-phenyl-3-(4-trifluoromethylphenoxy)propylamine.

3. A compound of claim 1 which is N-cyclopropylmethyl-N-methyl-3-phenyl-3-(4-trifluoromethylphenoxy)-propylamine.

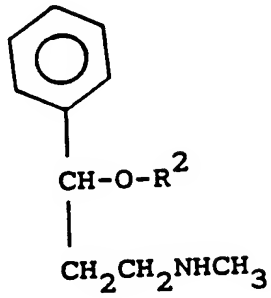
4. A compound of claim 1 which is N-butyl-N-methyl-3-phenyl-3-(5,6,7,8-tetrahydro-2-naphthoxy)-propylamine.

5. A compound of claim 1 which is N-butyl-3-(5-indanyloxy)-N-methyl-3-phenylpropylamine.

6. A compound of claim 1 which is N-cyclopropyl-N-methyl-3-phenyl-3-(3-trifluoromethylphenoxy)-propylamine.

7. A method of preparing a compound according to claim 1 **characterized by**

a) reacting a compound having the general formula II



(II)

wherein R^2 has the meaning defined above with a compound having the general formula R^1-X, wherein X is a leaving group such as halogen and R^1 has the meaning defined above, and
b) optionally reacting the product of step (a) with a pharmaceutically acceptable acid.

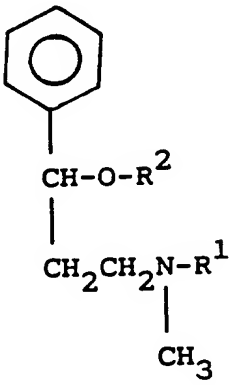
8. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically-acceptable carrier or diluent.

9. The pharmaceutical composition of claim 8 wherein it is in the form of an oral dosage unit containing 1 to 100 mg of the active compound.

10. Use of aryloxyphenylpropylamines according to claim 1 for the preparation of a medicament for treating an indication related to calcium overload in brain cells of mammals.

Claims for the following Contracting State : ES

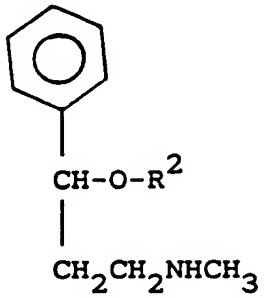
1. A method of preparing aryloxyphenylpropylamines having the general formula I



(I)

wherein
R^1 is C_{3-7}-cycloalkyl, C_{3-10}-alkyl or alkenyl which may be straight, branched or cyclic, unsubstituted or substituted with C_{1-4}-alkoxy, aryloxy or cycloalkyl or cycloalkylalkyl; and
R^2 is 3,4-methylenedioxyphenyl, aryl or heteroaryl, which are optionally substituted with one or more cyano, halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkenyl, trifluoromethyl, C_{3-5}-alkylene, aryloxy or aralkoxy;
or salts thereof with a pharmaceutically acceptable acid
characterized by

(a) reacting a compound having the general formula II



(II)

wherein R^2 has the meaning defined above with a compound having the general formula R^1-X, wherein X is a leaving group such as halogen and R^1 has the meaning defined above, and
(b) optionally reacting the product of step (a) with a pharmaceutically acceptable acid.

2. The method of claim 1 wherein the compound according to formula I is N-butyl-N-methyl-3-phenyl-3-(4-trifluoromethylphenoxy)propylamine.

3. The method of claim 1 wherein the compound according to formula I is N-cyclopropylmethyl-N-methyl-3-phenyl-3-(4-trifluoromethylphenoxy)propylamine.

4. The method of claim 1 wherein the compound according to formula I is N-butyl-N-methyl-3-phenyl-3-(5,6,7,8-tetrahydro-2-naphthoxy)propylamine.

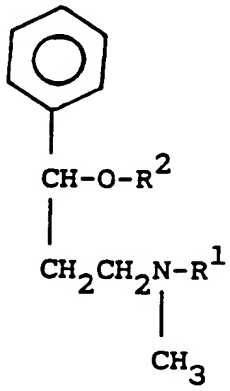
5. The method of claim 1 wherein the compound according to formula I is N-butyl-3-(5-indanyloxy)-N-methyl-3-phenylpropylamine.

6. The method of claim 1 wherein the compound according to formula I is N-cyclopropyl-N-methyl-3-phenyl-3-(3-trifluoromethylphenoxy)propylamine.

7. A method of preparing a pharmaceutical composition comprising formulating an aryloxyphenyl-proylamine prepared according to claim 1 with a pharmaceutically acceptable carrier or diluent.

8. The method of claim 7 wherein the pharmaceutical composition is prepared in the form of an oral dosage unit containing 1 to 100 mg of the active compound.

9. Use of aryloxyphenylpropylamines having the general formula I

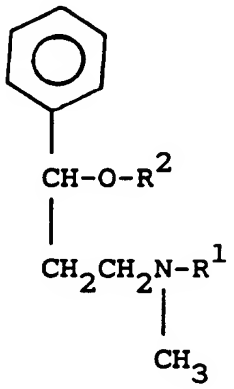


(I)

wherein in formula I, R^1 is C_{3-7}-cycloalkyl, C_{3-10}-alkyl or alkenyl which may be straight, branched or cyclic, unsubstituted or substituted with C_{1-4}-alkoxy, aryloxy or cycloalkyl or cycloalkylalkyl; and
R^2 is 3,4-methylenedioxyphenyl, aryl or heteroaryl, which are optionally substituted with one or more cyano, halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkenyl, trifluoromethyl, C_{3-5}-alkylene, aryloxy or aralkoxy;
or salts thereof with a pharmaceutically acceptable acid, for the preparation of a medicament for treating an indication related to calcium overload in brain cells of mammals.

Claims for the following Contracting State : GR

1. Aryloxyphenylpropylamines having the general formula I



(I)

wherein
R^1 is C_{3-7}-cycloalkyl, C_{3-10}-alkyl or alkenyl which may be straight, branched or cyclic, unsubstituted or substituted with C_{1-4}-alkoxy, aryloxy or cycloalkyl or cycloalkylalkyl; and
R^2 is 3,4-methylenedioxyphenyl, aryl or heteroaryl, which are optionally substituted with one or more cyano, halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkenyl, trifluoromethyl, C_{3-5}-alkylene, aryloxy or aralkoxy;
and salts thereof with a pharmaceutically acceptable acid.

2. A compound of claim 1 which is N-butyl-N-methyl-3-phenyl-3-(4-trifluoromethylphenoxy)propylamine.

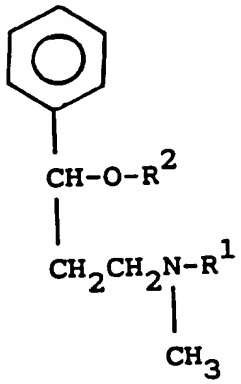
3. A compound of claim 1 which is N-cyclopropylmethyl-N-methyl-3-phenyl-3-(4-trifluoromethylphenoxy)-propylamine.

4. A compound of claim 1 which is N-butyl-N-methyl-3-phenyl-3-(5,6,7,8-tetrahydro-2-naphthoxy)-propylamine.

5. A compound of claim 1 which is N-butyl-3-(5-indanyloxy)-N-methyl-3-phenylpropylamine.

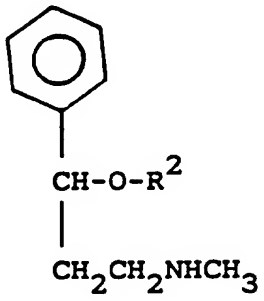
6. A compound of claim 1 which is N-cyclopropyl-N-methyl-3-phenyl-3-(3-trifluoromethylphenoxy)-propylamine.

7. A method of preparing aryloxyphenylpropylamines having the general formula I



(I)

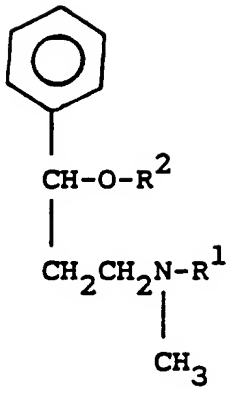
wherein
R^1 is C_{3-7}-cycloalkyl, C_{3-10}-alkyl or alkenyl which may be straight, branched or cyclic, unsubstituted or substituted with C_{1-4}-alkoxy, aryloxy or cycloalkyl or cycloalkylalkyl; and
R^2 is 3,4-methylenedioxyphenyl, aryl or heteroaryl, which are optionally substituted with one or more cyano, halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkenyl, trifluoromethyl, C_{3-5}-alkylene, aryloxy or aralkoxy;
or salts thereof with a pharmaceutically acceptable acid **characterized by**
(a) reacting a compound having the general formula II



(II)

wherein R^2 has the meaning defined above with a compound having the general formula R^1-X, wherein X is a leaving group such as halogen and R^1 has the meaning defined above, and
(b) optionally reacting the product of step (a) with a pharmaceutically acceptable acid.

8. A method of preparing a pharmaceutical composition comprising formulating an aryloxyphenylproplamine having the general formula I

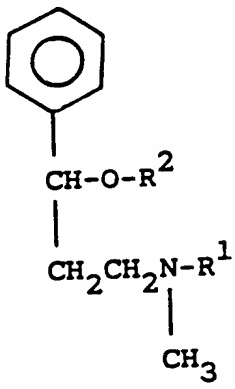


(I)

wherein
R^1 is C_{3-7}-cycloalkyl, C_{3-10}-alkyl or alkenyl which may be straight, branched or cyclic, unsubstituted or substituted with C_{1-4}-alkoxy, aryloxy or cycloalkyl or cycloalkylalkyl; and
R^2 is 3,4-methylenedioxyphenyl, aryl or heteroaryl, which are optionally substituted with one or more cyano, halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkenyl, trifluoromethyl, C_{3-5}-alkylene, aryloxy or aralkoxy;
and salts thereof, with a pharmaceutically acceptable carrier or diluent.

9. The method of claim 8 wherein the pharmaceutical composition is prepared in the form of an oral dosage unit containing 1 to 100 mg of the active compound.

10. Use of aryloxyphenylpropylamines having the general formula I



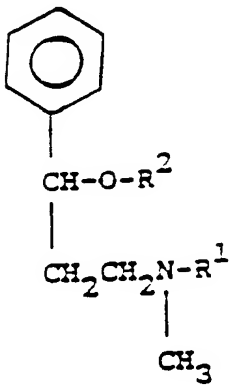
(I)

wherein in formula I, R^1 is C_{3-7}-cycloalkyl, C_{3-10}-alkyl or alkenyl which may be straight, branched or cyclic, unsubstituted or substituted with C_{1-4}-alkoxy, aryloxy or cycloalkyl or cycloalkylalkyl; and
R^2 is 3,4-methylenedioxyphenyl, aryl or heteroaryl, which are optionally substituted with one or more cyano, halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkenyl, trifluoromethyl, C_{3-5}-alkylene, aryloxy or aralkoxy;
or salts thereof with a pharmaceutically acceptable acid, for the preparation of a medicament for treating an indication related to calcium overload in brain cells of mammals.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Aryloxyphenylpropylamine mit der allgemeinen Formel I



(I)

worin
R^1 eine C_{3-7}-Cycloalkyl-, C_{3-10}-Alkyl- oder Alkenyl-Gruppe, welche gerade, verzweigt oder cyclisch, unsubstituiert oder mit einer C_{1-4}-Alkoxy-, Aryloxy- oder Cycloalkyl- oder Cycloalkylalkyl-Gruppe substituiert sein kann, ist;
und
R^2 eine 3,4-Methylendioxyphenyl-, Aryl- oder Heteroaryl-Gruppe, welche wahlweise mit einer oder mehreren Cyano-, Halogen-, C_{1-6}-Alkyl-, C_{1-6}-Alkoxy-, C_{1-6}-Alkenyl-, Trifluormethyl-, C_{3-5}-Alkylen-, Aryloxy- oder Aralkoxy-Gruppe(n) substituiert sind, ist;
und deren Salze mit einer pharmazeutisch annehmbaren Säure.

2. Verbindung nach Anspruch 1, welche N-Butyl-N-methyl-3-phenyl-3-(4-trifluormethylphenoxy)propylamin ist.

3. Verbindung nach Anspruch 1, welche N-Cyclopropylmethyl-N-methyl-3-phenyl-3-(4-trifluormethylphenoxy)propylamin ist.

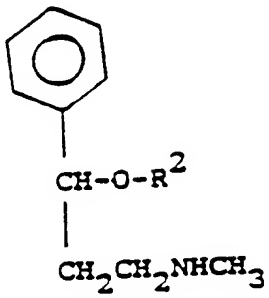
4. Verbindung nach Anspruch 1, welche N-Butyl-N-methyl-3-phenyl-3-(5,6,7,8-tetrahydro-2-naphthoxy)-propylamin ist.

5. Verbindung nach Anspruch 1, welche N-Butyl-3-(5-indanyloxy)-N-methyl-3-phenylpropylamin ist.

6. Verbindung nach Anspruch 1, welche N-Cyclopropyl-N-methyl-3-phenyl-3-(3-trifluormethylphenoxy)-propylamin ist.

7. Verfahren zum Herstellen einer Verbindung gemäß Anspruch 1, **gekennzeichnet durch**

a) Reagierenlassen einer Verbindung mit der allgemeinen Formel II



(II)

worin R^2 die vorstehend definierte Bedeutung hat mit einer Verbindung mit der allgemeinen Formel R^1-X, worin X eine austretende Gruppe, wie ein Halogen ist, und R^1 die vorstehend definierte Bedeutung hat,
und

b) wahlweise Reagierenlassen des Produkts aus Stufe (a) mit einer pharmazeutisch annehmbaren Säure.

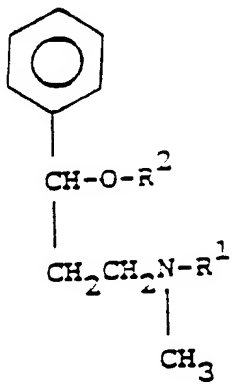
8. Pharmazeutische Zusammensetzung, umfassend eine Verbindung nach Anspruch 1 und einen pharmazeutisch annehmbaren Träger oder ein pharmazeutisch annehmbares Verdünnungsmittel.

9. Pharmazeutische Zusammensetzung nach Anspruch 8, worin diese in der Form einer oralen Dosierungseinheit, enthaltend 1 bis 100 mg der aktiven Verbindung, ist.

10. Verwendung von Aryloxyphenylpropylaminen nach Anspruch 1 für die Herstellung eines Medikamentes zum Behandeln einer Indikation, die mit einer Calciumüberladung in Gehirnzellen von Säugern in Beziehung steht.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zum Herstellen von Aryloxyphenylpropylaminen mit der allgemeinen Formel I

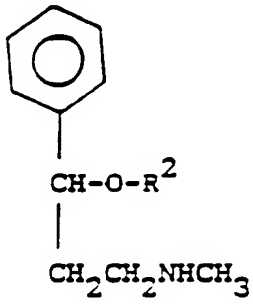


(I)

worin
R^1 eine C_{3-7}-Cycloalkyl-, C_{3-10}-Alkyl- oder Alkenyl-Gruppe, welche gerade, verzweigt oder cyclisch, unsubstituiert oder mit einer C_{1-4}-Alkoxy-, Aryloxy- oder Cycloalkyl- oder Cycloalkylalkyl-Gruppe substituiert sein kann, ist;
und

R^2 eine 3,4-Methylendioxyphenyl-, Aryl- oder Heteroaryl-Gruppe, welche wahlweise mit einer oder mehreren Cyano-, Halogen-, C_{1-6}-Alkyl-, C_{1-6}-Alkoxy-, C_{1-6}-Alkenyl-, Trifluormethyl-, C_{3-5}-Alkylen-, Aryloxy- oder Aralkoxy-Gruppe(n) substituiert sind, ist;
oder deren Salze mit einer pharmazeutisch annehmbaren Säure, **gekennzeichnet durch**

a) Reagierenlassen einer Verbindung mit der allgemeinen Formel II



(II)

worin R^2 die vorstehend definierte Bedeutung hat mit einer Verbindung mit der allgemeinen Formel R^1-X, worin x eine austretende Gruppe, wie ein Halogen ist, und R^1 die vorstehend definierte Bedeutung hat, und

b) wahlweise Reagierenlassen des Produkts aus Stufe (a) mit einer pharmazeutisch annehmbaren Säure.

2. Verfahren nach Anspruch 1, worin die Verbindung gemäß Formel I N-Butyl-N-methyl-3-phenyl-3-(4-trifluormethylphenoxy)propylamin ist.

3. Verfahren nach Anspruch 1, worin die Verbindung gemäß Formel I N-Cyclopropylmethyl-N-methyl-3-phenyl-3-(4-trifluormethylphenoxy)propylamin ist.

4. Verfahren nach Anspruch 1, worin die Verbindung gemäß Formel I N-Butyl-N-methyl-3-phenyl-3-(5,6,7,8-tetrahydro-2-naphthoxy)propylamin ist.

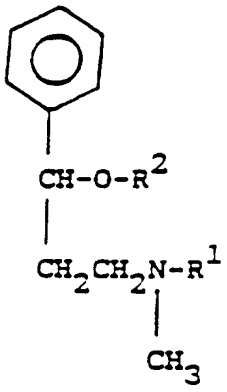
5. Verfahren nach Anspruch 1, worin die Verbindun gemäß Formel I N-Butyl-3-(5-indanyloxy)-N-methyl-3-phenylpropylamin ist.

6. Verfahren nach Anspruch 1, worin die Verbindung gemäß Formel I N-Cyclopropyl-N-methyl-3-phenyl-3-(3-trifluormethylphenoxy)propylamin ist.

7. Verfahren zum Herstellen einer pharmazeutischen Zusammensetzung, umfassend das Formulieren eines Aryloxyphenylpropylamins, hergestellt nach Anspruch 1,mit einem pharmazeutisch annehmbaren Träger oder Verdünnungsmittel.

8. Verfahren nach Anspruch 7, worin die pharmazeutische Zusammensetzung in der Form einer oralen Dosierungseinheit, enthaltend 1 bis 100 mg der aktiven Verbindung, hergestellt wird.

9. Verwendung von Aryloxyphenylpropylaminen mit der allgemeinen Formel I

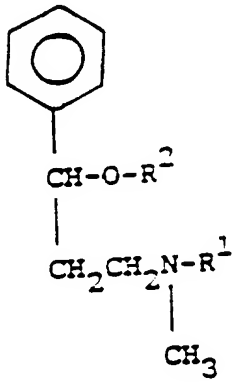


(I)

worin in Formel I
R^1 eine C_{3-7}-Cycloalkyl-, C_{3-10}-Alkyl- oder Alkenyl-Gruppe, welche gerade, verzweigt oder cyclisch, unsubstituiert oder mit einer C_{1-4}-Alkoxy-, Aryloxy- oder Cycloalkyl- oder Cycloalkylalkyl-Gruppe substituiert sein kann, ist;
und
R^2 eine 3,4-Methylendioxyphenyl-, Aryl- oder Heteroaryl-Gruppe, welche wahlweise mit einer oder mehreren Cyano-, Halogen-, C_{1-6}-Alkyl-, C_{1-6}-Alkoxy-, C_{1-6}-Alkenyl-, Trifluormethyl-, C_{3-5}-Alkylen-, Aryloxy- oder Aralkoxy-Gruppe(n) substituiert sind, ist;
und deren Salze mit einer pharmazeutisch annehmbaren Säure, für die Herstellung eines Medikamentes zum Behandeln einer Indikation, die mit einer Calciumüberladung in Gehirnzellen von Säugern in Beziehung steht.

Patentansprüche für folgenden Vertragsstaat : GR

1. Aryloxyphenylpropylamine mit der allgemeinen Formel I



(I)

worin
R^1 eine C_{3-7}-Cycloalkyl-, C_{3-10}-Alkyl- oder Alkenyl-Gruppe, welche gerade, verzweigt oder cyclisch, unsubstituiert oder mit einer C_{1-4}-Alkoxy-, Aryloxy- oder Cycloalkyl- oder Cycloalkylalkyl-Gruppe substituiert sein kann, ist;
und
R^2 eine 3,4-Methylendioxyphenyl-, Aryl- oder Heteroaryl-Gruppe, welche wahlweise mit einer oder mehreren Cyano-, Halogen-, C_{1-6}-Alkyl-, C_{1-6}-Alkoxy-, C_{1-6}-Alkenyl-, Trifluormethyl-, C_{3-5}-Alkylen-, Aryloxy- oder Aralkoxy-Gruppe(n) substituiert sind, ist;

und deren Salze mit einer pharmazeutisch annehmbaren Säure.

2. Verbindung nach Anspruch 1, welche N-Butyl-N-methyl-3-phenyl-3-(4-trifluormethylphenoxy)propylamin ist.

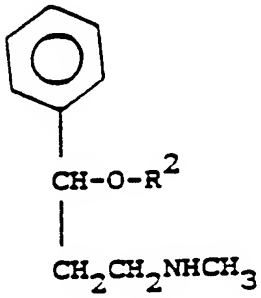
3. Verbindung nach Anspruch 1, welche N-Cyclopropylmethyl-N-methyl-3-phenyl-3-(4-trifluormethylphenoxy)propylamin ist.

4. Verbindung nach Anspruch 1, welche N-Butyl-N-methyl-3-phenyl-3-(5,6,7,8-tetrahydro-2-naphthoxy)-propylamin ist.

5. Verbindung nach Anspruch 1, welche N-Butyl-3-(5-indanyloxy)-N-methyl-3-phenylpropylamin ist.

6. Verbindung nach Anspruch 1, welche N-Cyclopropyl-N-methyl-3-phenyl-3-(3-trifluormethylphenoxy)-propylamin ist.

7. Verfahren zum Herstellen einer Verbindung gemäß Anspruch 1, **gekennzeichnet durch**
a) Reagierenlassen einer Verbindung mit der allgemeinen Formel II

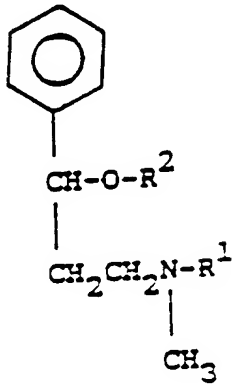


(II)

worin R^2 die vorstehend definierte Bedeutung hat mit einer Verbindung mit der allgemeinen Formel R^1-X, worin X eine austretende Gruppe, wie ein Halogen ist, und R^1 die vorstehend definierte Bedeutung hat,
und

b) wahlweise Reagierenlassen des Produkts aus Stufe (a) mit einer pharmazeutisch annehmbaren Säure.

8. Verfahren zum Herstellen einer pharmazeutischen Zusammensetzung, umfassend das Formulieren eines Aryloxyphenylpropylamins mit der allgemeinen Formel I

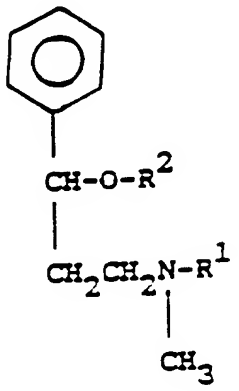


(I)

worin
R^1 eine C_{3-7}-Cycloalkyl-, C_{3-10}-Alkyl- oder Alkenyl-Gruppe, welche gerade, verzweigt oder cyclisch, unsubstituiert oder mit einer C_{1-4}-Alkoxy-, Aryloxy- oder Cycloalkyl- oder Cycloalkylalkyl-Gruppe substituiert sein kann, ist;
und
R^2 eine 3,4-Methylendioxyphenyl-, Aryl- oder Heteroaryl-Gruppe, welche wahlweise mit einer oder mehreren Cyano-, Halogen-, C_{1-6}-Alkyl-, C_{1-6}-Alkoxy-, C_{1-6}-Alkenyl-, Trifluormethyl-, C_{3-5}-Alkylen-, Aryloxy- oder Aralkoxy-Gruppe(n) substituiert sind, ist;
und deren Salze mit einem pharmazeutisch annehmbaren Träger oder Verdünnungsmittel.

9. Verfahren nach Anspruch 8, worin die pharmazeutische Zusammensetzung in der Form einer oralen Dosierungseinheit, enthaltend 1 bis 100 mg der aktiven Verbindung, hergestellt wird.

10. Verwendung von Aryloxyphenylpropylaminen mit der allgemeinen Formel I



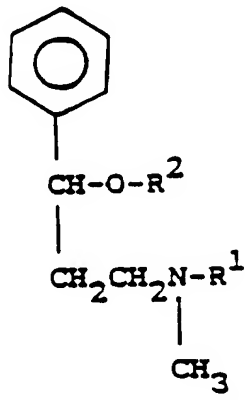
(I)

worin in Formel I
R^1 eine C_{3-7}-Cycloalkyl-, C_{3-10}-Alkyl- oder Alkenyl-Gruppe, welche gerade, verzweigt oder cyclisch, unsubstituiert oder mit einer C_{1-4}-Alkoxy-, Aryloxy- oder Cycloalkyl- oder Cycloalkylalkyl-Gruppe substituiert sein kann, ist;
und
R^2 eine 3,4-Methylendioxyphenyl-, Aryl- oder Heteroaryl-Gruppe, welche wahlweise mit einer oder mehreren Cyano-, Halogen-, C_{1-6}-Alkyl-, C_{1-6}-Alkoxy-, C_{1-6}-Alkenyl-, Trifluormethyl-, C_{3-5}-Alkylen-, Aryloxy- oder Aralkoxy-Gruppe(n) substituiert sind, ist;
und deren Salze mit einer pharmazeutisch annehmbaren Säure für die Herstellung eines Medikamentes zum Behandeln einer Indikation, die mit einer Calciumüberladung in Gehirnzellen von Säugern in Beziehung steht.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Aryloxyphénylpropylamines de formule générale I



(I)

où

R^1 est un radical cycloalkyle en C_{3-7}, alkyle en C_{3-10} ou alcényle, qui peut être linéaire, ramifié ou cyclique, non substitué ou substitué avec un radical alkoxy en C_{1-4}, aryloxy ou cycloalkyle ou cycloalkylalkyle ; et

R^2 est un radical 3,4-méthylènedioxyphényle, aryle ou hétéroaryle, qui sont éventuellement substitués avec un ou plusieurs cyano, halogène, alkyle en C_{1-6}, alkoxy en C_{1-6}, alcényle en C_{1-6}, trifluorométhyle, alkylène en C_{3-5}, aryloxy ou aralkoxy ;

et les sels de celles-ci avec un acide pharmaceutiquement acceptable.

2. Composé selon la revendication 1, qui est la N-butyl-N-méthyl-3-phényl-3-(4-trifluorométhylphénoxy)-propylamine.

3. Composé selon la revendication 1, qui est la N-cyclopropylméthyl-N-méthyl-3-phényl-3-(4-trifluorométhylphénoxy)propylamine.

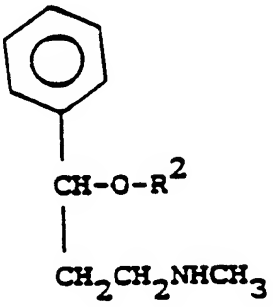
4. Composé selon la revendication 1, qui est la N-butyl-N-méthyl-3-phényl-3-(5,6,7,8-tétrahydro-2-naphtoxy)propylamine.

5. Composé selon la revendication 1, qui est la N-butyl-3-(5-indanyloxy)-N-méthyl-3-phénylpropylamine.

6. Composé selon la revendication 1, qui est la N-cyclopropyl-N-méthyl-3-phényl-3-(3-trifluorométhylphénoxy)propylamine.

7. Procédé de préparation d'un composé selon la revendication 1, **caractérisé par**

a) la réaction d'un composé de formule générale II



(II)

où R^2 a la signification définie ci-dessus, avec un composé de formule générale R^1-X, où X est un groupe qui part, comme un halogène, et R^1 a la signification définie ci-dessus, et
b) la réaction optionnelle du produit de l'étape (a) avec un acide pharmaceutiquement acceptable.

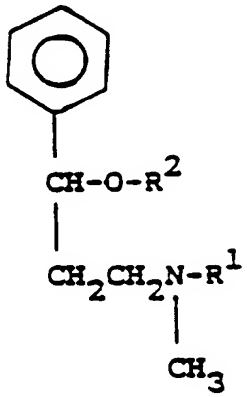
8. Composition pharmaceutique comprenant un composé selon la revendication 1 et un support ou un diluant pharmaceutiquement acceptables.

9. Composition pharmaceutique selon la revendication 8, où elle est sous la forme d'une unité galénique orale contenant 1 à 100 mg du composé actif.

10. Utilisation d'aryloxyphénylpropylamines selon la revendication 1, pour la préparation d'un médicament pour traiter une maladie liée à une surcharge en calcium dans les cellules du cerveau de mammifères.

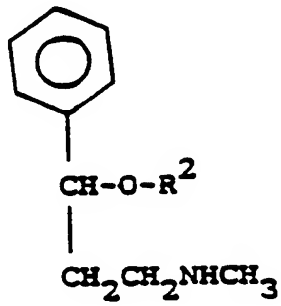
Revendications pour l'Etat contractant suivant : ES

1. Procédé de préparation d'aryloxyphénylpropylamines de formule générale I



(I)

où
R^1 est un radical cycloalkyle en C_{3-7}, alkyle en C_{3-10} ou alcényle, qui peut être linéaire, ramifié ou cyclique, non substitué ou substitué avec un radical alkoxy en C_{1-4}, aryloxy ou cycloalkyle ou cycloalkylalkyle ; et
R^2 est un radical 3,4-méthylènedioxyphényle, aryle ou hétéroaryle, qui sont éventuellement substitués avec un ou plusieurs cyano, halogène, alkyle en C_{1-6}, alkoxy en C_{1-6}, alcényle en C_{1-6}, trifluorométhyle, alkylène en C_{3-5}, aryloxy ou aralkoxy ;
ou de sels de celles-ci avec un acide pharmaceutiquement acceptable
caractérisé par
a) la réaction d'un composé de formule générale II



(II)

où R^2 a la signification définie ci-dessus, avec un composé de formule générale R^1-X, où X est un groupe qui part, comme un halogène, et R^1 a la signification définie ci-dessus, et
b) la réaction optionnelle du produit de l'étape (a) avec un acide pharmaceutiquement acceptable.

2. Procédé selon la revendication 1, dans lequel le composé selon la formule I est la N-butyl-N-méthyl-3-phényl-3-(4-trifluorométhylphénoxy)propylamine.

3. Procédé selon la revendication 1, dans lequel le composé selon la formule I est la N-cyclopropylméthyl-N-méthyl-3-phényl-3-(4-trifluorométhylphénoxy)propylamine.

4. Procédé selon la revendication 1, dans lequel le composé selon la formule I est la N-butyl-N-méthyl-3-phényl-3-(5,6,7,8-tétrahydro-2-naphtoxy)propylamine.

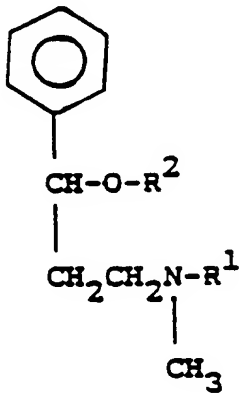
5. Procédé selon la revendication 1, dans lequel le composé selon la formule I est la N-butyl-3-(5-indanyloxy)-N-méthyl-3-phénylpropylamine.

6. Procédé selon la revendication 1, dans lequel le composé selon la formule I est la N-cyclopropyl-N-méthyl-3-phényl-3-(3-trifluorométhylphénoxy)propylamine.

7. Procédé de préparation d'une composition pharmaceutique comprenant la formulation d'une aryloxyphénylpropylamine préparée selon la revendication 1 avec un support ou un diluant pharmaceutiquement acceptables.

8. Procédé selon la revendication 7, dans lequel la composition pharmaceutique est préparée sous la forme d'une unité galénique orale contenant 1 à 100 mg du composé actif.

9. Utilisation d'aryloxyphénylpropylamines de formule générale I

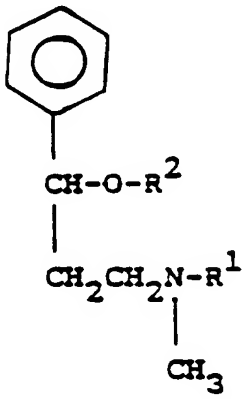


(I)

où, dans la formule I, R^1 est un radical cycloalkyle en C_{3-7}, alkyle en C_{3-10} ou alcényle, qui peut être linéaire, ramifié ou cyclique, non substitué ou substitué avec un radical alkoxy en C_{1-4}, aryloxy ou cycloalkyle ou cycloalkylalkyle ; et
R^2 est un radical 3,4-méthylènedioxyphényle, aryle ou hétéroaryle, qui sont éventuellement substitués avec un ou plusieurs cyano, halogène, alkyle en C_{1-6}, alkoxy en C_{1-6}, alcényle en C_{1-6}, trifluorométhyle, alkylène en C_{3-5}, aryloxy ou aralkoxy ;
ou de sels de celles-ci avec un acide pharmaceutiquement acceptable, pour la préparation d'un médicament pour traiter une maladie liée à une surcharge en calcium dans les cellules du cerveau de mammifères.

Revendications pour l'Etat contractant suivant : GR

1. Aryloxyphénylpropylamines de formule générale I



(I)

où
R^1 est un radical cycloalkyle en C_{3-7}, alkyle en C_{3-10} ou alcényle, qui peut être linéaire, ramifié ou cyclique, non substitué ou substitué avec un radical alkoxy en C_{1-4}, aryloxy ou cycloalkyle ou cycloalkylalkyle ; et
R^2 est un radical 3,4-méthylènedioxyphényle, aryle ou hétéroaryle, qui sont éventuellement substitués avec un ou plusieurs cyano, halogène, alkyle en C_{1-6}, alkoxy en C_{1-6}, alcényle en C_{1-6}, trifluorométhyle, alkylène en C_{3-5}, aryloxy ou aralkoxy ;
et les sels de celles-ci avec un acide pharmaceutiquement acceptable.

2. Composé selon la revendication 1, qui est la N-butyl-N-méthyl-3-phényl-3-(4-trifluorométhylphénoxy)-propylamine.

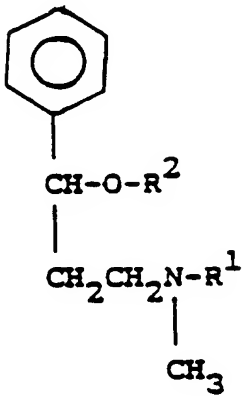
3. Composé selon la revendication 1, qui est la N-cyclopropylméthyl-N-méthyl-3-phényl-3-(4-trifluorométhylphénoxy)propylamine.

4. Composé selon la revendication 1, qui est la N-butyl-N-méthyl-3-phényl-3-(5,6,7,8-tétrahydro-2-naphtoxy)propylamine.

5. Composé selon la revendication 1, qui est la N-butyl-3-(5-indanyloxy)-N-méthyl-3-phénylpropylamine.

6. Composé selon la revendication 1, qui est la N-cyclopropyl-N-méthyl-3-phényl-3-(3-trifluorométhylphénoxy)propylamine.

7. Procédé de préparation d'aryloxyphénylpropylamines de formule générale I



(I)

où

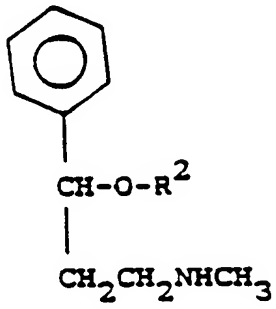
R^1 est un radical cycloalkyle en C_{3-7}, alkyle en C_{3-10} ou alcényle, qui peut être linéaire, ramifié ou cyclique, non substitué ou substitué avec un radical alkoxy en C_{1-4}, aryloxy ou cycloalkyle ou cycloalkylalkyle ; et

R^2 est un radical 3,4-méthylènedioxyphényle, aryle ou hétéroaryle, qui sont éventuellement substitués avec un ou plusieurs cyano, halogène, alkyle en C_{1-6}, alkoxy en C_{1-6}, alcényle en C_{1-6}, trifluorométhyle, alkylène en C_{3-5}, aryloxy ou aralkoxy ;

ou de sels de celles-ci avec un acide pharmaceutiquement acceptable,

caractérisé par

a) la réaction d'un composé de formule générale II

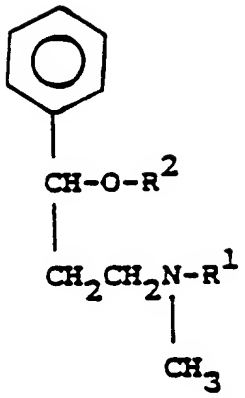


(II)

où R^2 a la signification définie ci-dessus, avec un composé de formule générale R^1-X, où X est un groupe qui part, comme un halogène, et R^1 a la signification définie ci-dessus, et

b) la réaction optionnelle du produit de l'étape (a) avec un acide pharmaceutiquement acceptable.

8. Procédé de préparation d'une composition pharmaceutique comprenant la formulation d'une aryloxyphénylpropylamine de formule générale I

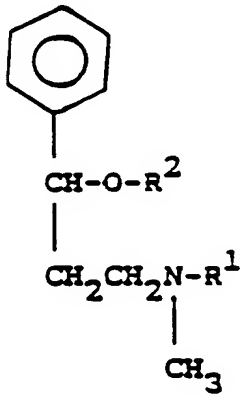


(I)

où
R^1 est un radical cycloalkyle en C_{3-7}, alkyle en C_{3-10} ou alcényle, qui peut être linéaire, ramifié ou cyclique, non substitué ou substitué avec un radical alkoxy en C_{1-4}, aryloxy ou cycloalkyle ou cycloalkylalkyle ; et
R^2 est un radical 3,4-méthylènedioxyphényle, aryle ou hétéroaryle, qui sont éventuellement substitués avec un ou plusieurs cyano, halogène, alkyle en C_{1-6}, alkoxy en C_{1-6}, alcényle en C_{1-6}, trifluorométhyle, alkylène en C_{3-5}, aryloxy ou aralkoxy ;
et de sels de celles-ci, avec un support ou un diluant pharmaceutiquement acceptables.

9. Procédé selon la revendication 8, dans lequel la composition pharmaceutique est préparée sous la forme d'une unité galénique orale contenant 1 à 100 mg du composé actif.

10. Utilisation d'aryloxyphénylpropylamines de formule générale I



(I)

où, dans la formule I, R^1 est un radical cycloalkyle en C_{3-7}, alkyle en C_{3-10} ou alcényle, qui peut être linéaire, ramifié ou cyclique, non substitué ou substitué avec un radical alkoxy en C_{1-4}, aryloxy ou cycloalkyle ou cycloalkylalkyle ; et
R^2 est un radical 3,4-méthylènedioxyphényle, aryle ou hétéroaryle, qui sont éventuellement substitués avec un ou plusieurs cyano, halogène, alkyle en C_{1-6}, alkoxy en C_{1-6}, alcényle en C_{1-6}, trifluorométhyle, alkylène en C_{3-5}, aryloxy ou aralkoxy ;
ou de sels de celles-ci avec un acide pharmaceutiquement acceptable, pour la préparation d'un médicament pour traiter une maladie liée à une surcharge en calcium dans les cellules du cerveau de mammifères.